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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/518,701
Filing Date: September 01, 2005
Appellant(s): LEVINSON ET AL.

Daniel M. Scolnick
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 1, 2010 appealing from the Office action mailed April 7, 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-3, 5-8, 22-24, 26-29, 32-37, and 50-73 are rejected in this application.

Claims 1-3, 5-8, 22-24, 26-29, 32-37, and 50-73 are pending in this application.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,629,415	Hollis et al.	5-1997
4,769,326	Rutter	9-1988
US2002/0172673	Klysner et al.	11-2002

Chen et al., WO 98/53843

Wang et al., WO 99/67293

WO 02/20038

Walls et al., Nucleic Acids Research, 1993, 21:2921-2929

Janeway et al., Immunobiology, 3rd edition, Garland Publishing, 1997, 3:26-3:31

Muller et al., J. Immunol. 1983, 131:877-881

Jabara et al., J. Immunol., 1993, 151:4528-4533

Chu et al., J. Exp. Med., 1993, 178:1381-1390

Watson et al., Molecular Biology of the Gene, 4th edition, 1987, Benjamin Cummings Publishing Company, Inc., pages 860, 866, and 875.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1-3, 5-7, 22-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent 4,769,326).

Chen et al. disclose vaccine constructs comprising the membrane bound domain of IgE coupled to heterologous sequences and excipients (see entire document, particularly the abstract and pages 3-5). These constructs are disclosed as being made recombinantly using vectors and host cells (see page 5). Note that heterologous antigens comprise helper T epitopes, and that Chen et al. disclose that their products are to be used in the suppression of IgE mediated responses, such as those that occur in allergy (see page 2).

The disclosure of Chen et al. differs from the instant claimed invention in that the nucleic acids of Chen et al. are not disclosed as being administered to a patient (i.e. the nucleic acids are not disclosed as a vaccine) nor are they disclosed as comprising a proteolytic cleavage sequence.

Wang et al. disclose vaccine constructs wherein IgE sequence is coupled to T helper epitopes such as those from tetanus toxoid, and wherein the administered construct is a nucleic acid (see entire document, particularly the abstract and pages 11, 13-14, 16, 20, 39-40). T helper epitopes from tetanus toxoid are preferred because they comprise the advantageous property of being promiscuous T helper epitopes that can be recognized by most members of a population expressing diverse MHC haplotypes (see particularly pages 16, 17, and 33). Wang et al. further disclose the desirability of inserting a linker sequence between IgE and T helper epitopes, such linkers offering the advantage of disrupting artificial secondary structures that result from directly joining the C-terminus of one epitope directly to the N-terminus of the other epitope and the

advantage of acting as a flexible hinge that allows for more effective interactions with immune cells (see particularly page 32).

Hollis et al. disclose that recombinant IgE encoding polynucleotides can be inserted in to plasmid vectors and used to generate a wide variety of host cells including bacterial and mammalian cells (see entire document, particularly columns 4-7). Such host cells can be used to express polypeptides, with antibodies specific for the IgE constructs being used for affinity purification of the expressed polypeptide (see column 7).

Rutter discloses that the use of linkers comprising proteolytic cleavage sites is desirable in the manufacture of fusion constructs since said linkers allow for the efficient incorporation and removal of desired functional properties (see entire document, particularly the abstract). Such linkers allow for the separation the component parts of the fusion protein without otherwise causing degradation or proteolysis to the proteins or peptides of interest (see particularly columns 7, 8, 10, and 12).

Therefore, it would have been obvious to a person of ordinary skill at the time the instant invention was made to modify the nucleic acid constructs of Chen et al. to comprise promiscuous tetanus toxoid T helper epitopes so that they could be used in nucleic acid vaccines that would be effective in a majority of individuals in populations comprising diverse MHC haplotypes. Note that the use of nucleic acid vaccines was well known and routine in the art as disclosed by Wang et al. Such vaccines could be propagated in bacterial host cells as disclosed by Hollis et al. due to their ease of manufacture. A person of ordinary skill in the art would have been further motivated to

incorporate proteolytic cleavage sequence linkers into such constructs since separation of epitopes provides the advantages of reduced unwanted secondary structure and increased flexibility as disclosed by Wang et al. and provides the advantage of allowing the component epitopes to be easily separated without excessive proteolytic degradation as disclosed by Rutter.

B. Claims 1-3, 5-7, 22-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

The '038 document discloses nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire document, particularly the abstract and pages 37 and 41). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly page 30). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly pages 52-56 and 66-67). The nucleic acids of the '038 document are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly pages 60-66). These teachings differ from the claimed invention in that they do not disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes.

Wang et al. disclose vaccine constructs wherein IgE sequence is coupled to T helper epitopes such as those from tetanus toxoid, and wherein the administered construct is a nucleic acid (see entire document, particularly the abstract and pages 11,

13-14, 16, 20, 39-40). T helper epitopes from tetanus toxoid are preferred because they comprise the advantageous property of being promiscuous T helper epitopes that can be recognized by most members of a population expressing diverse MHC haplotypes (see particularly pages 16, 17, and 33). Wang et al. further disclose the desirability of inserting a linker sequence between IgE and T helper epitopes, such linkers offering the advantage of disrupting artificial secondary structures that result from directly joining the C-terminus of one epitope directly to the N-terminus of the other epitope and the advantage of acting as a flexible hinge that allows for more effective interactions with immune cells (see particularly page 32).

Rutter discloses that the use of linkers comprising proteolytic cleavage sites is desirable in the manufacture of fusion constructs since said linkers allow for the efficient incorporation and removal of desired functional properties (see entire document, particularly the abstract). Such linkers allow for the separation the component parts of the fusion protein without otherwise causing degradation or proteolysis to the proteins or peptides of interest (see particularly columns 7, 8, 10, and 12).

Therefore, it would have been obvious to a person of ordinary skill at the time the instant invention was made to modify the nucleic acid constructs of the '038 document to comprise proteolytic cleavage sequence linkers since separation of epitopes provides the advantages of reduced unwanted secondary structure and increased flexibility as disclosed by Wang et al. and provides the advantage of allowing the component epitopes to be easily separated without excessive proteolytic degradation as disclosed by Rutter.

C. Claims 1-3, 5-7, 22-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Klysner et al. disclose nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire document, particularly the abstract and paragraphs 121 and 132). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly paragraph 101). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly paragraphs 171- 180 and 214-219). The nucleic acids of Klysner et al. are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly paragraphs 198-213). This disclosure differs from the claimed invention in that Klysner et al. do not disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes.

Wang et al. disclose vaccine constructs wherein IgE sequence is coupled to T helper epitopes such as those from tetanus toxoid, and wherein the administered construct is a nucleic acid (see entire document, particularly the abstract and pages 11, 13-14, 16, 20, 39-40). T helper epitopes from tetanus toxoid are preferred because they comprise the advantageous property of being promiscuous T helper epitopes that can be recognized by most members of a population expressing diverse MHC haplotypes (see particularly pages 16, 17, and 33). Wang et al. further disclose the desirability of

inserting a linker sequence between IgE and T helper epitopes, such linkers offering the advantage of disrupting artificial secondary structures that result from directly joining the C-terminus of one epitope directly to the N-terminus of the other epitope and the advantage of acting as a flexible hinge that allows for more effective interactions with immune cells (see particularly page 32).

Rutter discloses that the use of linkers comprising proteolytic cleavage sites is desirable in the manufacture of fusion constructs since said linkers allow for the efficient incorporation and removal of desired functional properties (see entire document, particularly the abstract). Such linkers allow for the separation the component parts of the fusion protein without otherwise causing degradation or proteolysis to the proteins or peptides of interest (see particularly columns 7, 8, 10, and 12).

Therefore, it would have been obvious to a person of ordinary skill at the time the instant invention was made to modify the nucleic acid constructs of Klysner et al. to comprise proteolytic cleavage sequence linkers since separation of epitopes provides the advantages of reduced unwanted secondary structure and increased flexibility as disclosed by Wang et al. and provides the advantage of allowing the component epitopes to be easily separated without excessive proteolytic degradation as disclosed by Rutter.

D and E. Claims 8, 32-37, 50, and 58-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent

4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The inventions rendered obvious by the disclosures of Chen et al., Wang et al. Hollis et al., and Rutter have been discussed above and differ from the claimed invention in that while they disclose the recombinant production of secreted polypeptides, they do not specify that the leader sequence used in such constructs is "an IgE leader sequence".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides. Note that as evidenced

by Janeway et al., the variable domains of immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an “IgE leader” is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. The recombined V(D)J variable domain and its attendant upstream leader sequence are not altered by the process of isotype switching. Therefore, the "Ig leader" of Walls et al. is an "IgE leader".

F and G. Claims 8, 32-37, 50, and 58-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The inventions rendered obvious by the disclosures of the ‘038 document, Wang et al., and Rutter have been discussed above and differ from the claimed invention in that while they disclose the recombinant production of secreted polypeptides, they do not specify that the leader sequence used in such constructs is "an IgE leader sequence".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides. Note that as evidenced by Janeway et al., the variable domains of immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an “IgE leader” is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. The recombined V(D)J variable

domain and its attendant upstream leader sequence are not altered by the process of isotype switching. Therefore, the "Ig leader" of Walls et al. is an "IgE leader".

H and I. Claims 8, 32-37, 50, and 58-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The inventions rendered obvious by the disclosures of Klysner et al., Wang et al., and Rutter have been discussed above and differ from the claimed invention in that while they disclose the recombinant production of secreted polypeptides, they do not specify that the leader sequence used in such constructs is "an IgE leader sequence".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides. Note that as evidenced by Janeway et al., the variable domains of immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an "IgE leader" is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. The recombined V(D)J variable domain and its attendant upstream leader sequence are not altered by the process of isotype switching. Therefore, the "Ig leader" of Walls et al. is an "IgE leader".

J. Claims 8, 32-37, and 66-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Klysner et al. disclose nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire

document, particularly the abstract and paragraphs 121 and 132). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly paragraph 101). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly paragraphs 171- 180 and 214-219). The nucleic acids of Klysner et al. are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly paragraphs 198-213). This disclosure differs from the instant claimed invention in that it is not specified that the leader sequence used for the expression of soluble polypeptides is an "IgE leader".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient

expression of Ig constructs, such as the chimeric IgE polypeptides of Klysner et al. Note that as evidenced by Janeway et al., the variable domains of immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an “IgE leader” is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. The recombined V(D)J variable domain and its attendant upstream leader sequence are not altered by the process of isotype switching. Therefore, the "Ig leader" of Walls et al. is an "IgE leader".

L. Claims 8, 32-37, and 66-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The ‘038 document discloses nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire document, particularly the abstract and pages 37 and 41). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly page 30). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly pages 52-56 and 66-67). The nucleic acids of

the '038 document are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly pages 60-66). This disclosure differs from the instant claimed invention in that it is not specified that the leader sequence used for the expression of soluble polypeptides is an "IgE leader".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as the chimeric IgE polypeptides of the '038 document. Note that as evidenced by Janeway et al., the variable domains of immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable

domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an “IgE leader” is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. The recombined V(D)J variable domain and its attendant upstream leader sequence are not altered by the process of isotype switching. Therefore, the "Ig leader" of Walls et al. is an "IgE leader".

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

The rejection of claim 50 under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31) has been withdrawn. As such, appellant's arguments labeled as K have been rendered moot and will not be addressed further.

The rejection of claim 50 under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31) has been withdrawn. As such, appellant's arguments labeled as M have been rendered moot and will not be addressed further.

(10) Response to Argument

A. Rejection of claims 1-3, 5-7, 22-24, and 26-29 under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent 4,769,326).

Appellant argues on pages 13-16 of the brief that the cited reference teach away from the instant claimed invention. Appellant believes this to be so because neither Chen et al. nor Wang et al. disclose constructs comprising cleavable linker sequences. Applicant further argues on page 15 of the brief that "Additionally, the Chen reference states that for conjugates in human use one would expect that there would be "no inhibition of IgE responses to *unrelated, unconjugated* antigens." (Chen, p. 10, line 22, emphasis added.)." Applicant furthers this argument by stating that "When introduced into physiological conditions the cleavage sequence would be cleaved by a protease and lead to unrelated, unconjugated antigens, which Chen teaches will lead to an undesirable result. Therefore, one of skill in the art reading the Chen reference in its entirety would not have inserted a proteolytic cleavage sequence because such a construct would lead to an unconjugated composition leading to a result that is explicitly not desired by the Chen reference."

This argument is not persuasive. First, appellant has claimed products (nucleic acids and host cells) and has not claimed methods of administration of said products to treat some particular disease or disorder. Second, appellant is reminded that motivations other than those of appellant can be used in a finding of obviousness.

Third, as has been pointed out during prosecution, there is no recited requirement that the fusion protein encoded by the claimed polynucleotide separates into two separate molecules upon expression in vivo and the specification does not define or limit the term "proteolytic cleavage sequence" to only those cleaved under physiological conditions. As such, appellant is arguing limitations not presently claimed. Specifically, appellant has argued that "when introduced into physiological conditions the cleavage sequence would be cleaved by a protease" yet this narrowed interpretation of the claimed product is not supported by the claims themselves or any definition in the specification. As stated in the rejection of record, an ordinary artisan would have been motivated to add a cleavage sequence between the components of a fusion protein as an aid in the construction of said fusion protein since they allow for the efficient incorporation and removal of functional properties as disclosed by Rutter et al. As was also discussed during prosecution, many of the enzymes contemplated for use by Rutter et al., such as Aspergillopeptidase B, are not proteins expressed in IgE-producing animals (see for example columns 15-16 of Rutter et al.) and thus a fusion polypeptide comprising a "proteolytic cleavage sequence" recognized Aspergillopeptidase B would not subject to cleavage under physiological conditions. Thus, the possibility that components of the fusion protein can be separated does not mean that they will be separated. Further, given that appellant has claimed products and not methods of treatment, and Rutter et al. set forth a reasonable reason why a proteolytic cleavage sequence would be of use to ordinary artisans when making fusion constructs, applicant arguments concerning "teaching away" by Chen et al are not persuasive.

Appellant also argues that Wang et al. teach away from the claimed invention in that Wang et al. disclose that the components are adjacent in order to evoke an efficient antibody response.

This argument is not persuasive because as with the Chen et al. reference, appellant has construed the "proteolytic cleavage sequence" to be limited only to those which can be cleaved in vivo under physiological conditions. Such an interpretation is not supported by reading the instant claims or by way of definition in the instant specification as has been discussed above.

Appellant has argued that the examiner's analysis of the proper scope of the claimed invention concerning proteolytic cleavage sequences "is reading the limitation out of the claims".

This argument is not persuasive. As stated above, neither the specification nor the claims limit "proteolytic cleavage sequences" to only those which can be cleaved under physiological conditions in vivo. Rutter et al. provides guidance and motivation to ordinary artisans as to why they would wish to incorporate such linkers into their fusion constructs. As such, the limitation has not been "read out" since an ordinary artisan would still have motivation, and an expectation of success in making a fusion protein which comprises a cleavable linker sequence. Therefore, appellant's arguments are not persuasive.

B. Rejection of claims 1-3, 5-7, 22-24, and 26-29 under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Appellant argues that Klysner et al. and Wang et al. teach away from the instant claimed invention. Appellant argues that Wang et al. teach away for the reasons discussed in part A. These reasons are not persuasive as was discussed above and will not be further addressed.

With regard to Klysner, appellant believes this document also teaches away because Klysner discloses that the epitopes should be simultaneously presented to the antigen presenting cells. Appellant argues that inclusion of a proteolytic cleavage sequence would eliminate the likelihood that simultaneous presentation could occur.

This argument is not persuasive for the reasons already discussed. Specifically, appellant's arguments concerning the scope of the claimed invention are too narrow and incorporate limitations not claimed. Further, appellant has not provided any evidence to support the assertion that a proteolytic cleavage sequence would impact simultaneous epitope presentation. Indeed, neither the claims nor the specification identify the protease(s) which act on the recited "proteolytic cleavage sequence" or where such proteases may be located in the body (if indeed they are present there at all). Thus, on what evidence does appellant make the assertion that the presence of a "proteolytic cleavage sequence" is deleterious to simultaneous epitope presentation? The '038 reference (Klysner et al.) discloses on pages 9-11 that antigen presenting cells proteolytically process exogenous antigens for presentation to T cells of the immune

system. As such, all polypeptides, including fusion proteins, are proteolytically cleaved into epitopes inside an antigen presenting cell. Thus, why would the presence of sequence cleavable by an unknown and unspecified protease necessarily lead to different epitopes of an exogenous antigen being internalized at different times by an antigen presenting cell?

C. Rejection of claims 1-3, 5-7, 22-24, and 26-29 under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326).

Appellant argues that Klysner et al. and Wang et al. teach away from the instant claimed invention. It should be noted that WO 02/20038 and (US2002/0172673) are the same document, differing only in pagination and the date of availability as prior art. As such, appellant's arguments and the reasons why such arguments are not persuasive are the same as those previously discussed in part B above.

D. Rejection of claims 8, 32-37, 50, and 58-73 under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant argues that the combination of references fails to teach all of the elements of the claims. Specifically, appellant argues that there is no evidence that the "Ig leader" of Walls et al. is in fact an "IgE leader". The declaration of inventor David B. Weiner was entered into the record on April 7, 2009 in an attempt to establish distinctiveness between the sequence disclosed by Walls et al. and that of the present claimed invention. Appellant believes that the examiner dismissed the declaration of inventor David B. Weiner without a reasonable basis to support such conclusions.

This argument is not persuasive. As was stated during prosecution, the declaration of David B. Weiner provides an alignment of sequences which are purported to be the leader sequences of immunoglobulins. The source of these sequences, such as GenBank accession numbers, or what organism(s) they are from are not provided. Further, some of the sequences are described as being "IgA constant" and "IgG constant". The constant domain is not expressed as a separate polypeptide in vivo and is always joined to the variable domain of immunoglobulin assembled via the process of V(D)J recombination. As such it is unclear how or why inventor Weiner has chosen the labels attached to the sequences of the alignment.

As shown in figures 3.26 and 3.28 of Janeway et al., the leader sequence is upstream of the variable domain and this same assembly can be joined to multiple distinct constant domains via the process of isotype/class switching. It is well known in the art that hybridomas expressing a monoclonal antibody can undergo class switching upon exposure to exogenous agents, such as IL-4 (Muller et al., Jabara et al., and Chu et al.). This allows researchers to construct families of antibodies whose members

differ from each other only in their heavy chain isotype (see particularly the left column of page 877 of Muller et al.). The variable domain and its attached leader sequence do not change even though the heavy chain isotype is changed. As such, there cannot be a leader that is an "IgE" leader since any given rearranged immunoglobulin locus (which initially is expressed with an IgM isotype) has the potential to class switch to IgE and secrete IgE rather than IgM.

As shown by Watson et al., there are approximately 250 different heavy chain locus V genes which can participate the process of V(D)J recombination (page 866 and table 23-3). Each V gene has its own leader sequence, as is made explicitly clear in figure 23-26 of Watson et al. Thus, there are potentially 250 distinct leader sequences that may be present in a rearranged immunoglobulin gene. Thus, finding that the leader of a sequence deposited in a database as an IgE antibody is different from the leader from another sequence deposited as an IgG1 antibody is only reflective of the diversity of leader sequences present in the heavy chain V genes and has no bearing on constant domain isotype since the same V(D)J rearranged sequence can be present with any heavy chain constant domain due to isotype switching (see figure 23.36 of Watson et al.).

Appellant has argued that the declaration provides evidence that not all leader sequences are the same. This is a given considering that according to Watson et al., there are about 250 distinct V genes for the heavy chain and thus there are theoretically 250 distinct immunoglobulin leader sequences. As such, appellant seems to have missed the point, which is that given basic B cell biology which is found in textbooks, is

explained above, and would be well known to ordinary artisans, **any** rearranged heavy chain variable domain (including its upstream leader sequence) can ultimately be associated with IgE through the process known in the art as isotype/class switching. The declaration does not identify any hallmarks which an ordinary artisan could use to identify an “IgE leader” and neither the specification nor the claims define this term to be limited to a specific amino acid sequence identified by a SEQ ID number. Further, the declaration does not provide any evidence that there is any functional difference between any of the leader sequences listed in the declaration. It is the examiner’s position that given basic B cell biology and class switching, it would not be possible for an artisan to discern any sequence or structural hallmarks which would allow for differentiation of an "IgE leader" from any other immunoglobulin leader since all “IgE” leaders originally were “IgM” leaders since IgM is the isotype expressed in naive B cells and other isotypes, such as IgG, IgA, and IgE can only ever be expressed by B cells which have undergone class switching in response to the local cytokine environment. See particularly page 875 and Figure 23-36 of Watson et al. Given that all of the aforementioned information concerning B cell biology and references were provided to appellant to rebut the assertions of the inventor’s declaration, and that such information can be found in introductory immunology textbooks, appellant’s conclusion that said declaration was summarily dismissed is erroneous.

E. Rejection of claims 50, 58, and 59-65 under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) in

view of Hollis et al. (US 5,629,415) and in view of Rutter (US Patent 4,769,326) and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant has separately argued these claims on grounds in addition to those presented in section D. It should be noted that these claims argued separately by appellant have not been rejected separately, thus leading to the nomenclature of "D and E" in the grounds of rejection presented in section (9) above.

Appellant repeats the arguments, already made by appellant in regards to ground of rejection A, that Chen et al. and Wang et al. teach away from the instant claimed invention. No new arguments, such as reasons why it is unexpected to combine "proteolytic cleavage sequences" and "IgE leader sequences" are presented.

Appellant's arguments concerning "teaching away" have been previously addressed in section A above. It should be noted that the ground of rejection indicated as "D and E" is an obviousness rejection based upon an earlier rejection set forth under 35 USC 103(a), and that the argument presented as E is the same argument presented to rebut said earlier rejection under 35 USC 103(a). Given that no new arguments are presented, this issue will not be addressed further.

F. Rejection of claims 8, 32-37, 50, and 58-73 under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293, of record) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29

above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant presents the same arguments as are detailed in D concerning appellant's allegation that the examiner summarily dismissed declaration evidence provided by one of the inventors concerning "IgE leader" sequences. The examiner's response to the allegations are presented in part D and will not be elaborated further.

G. Rejection of claims 50 and 58-65 under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Wang et al. (WO 99/67293, of record) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant has separately argued these claims even though they are part of the same rejection initially discussed in F. Appellant repeats the argument from B that the rejection is improper because Klysner et al. and Wang et al. teach away from the claimed invention.

This argument is not persuasive for the reasons already discussed in B.

H. Rejection of claims 8, 32-37, 50, and 58-73 under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO

99/67293) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant argues the same grounds as in D. Note that WO/20038 and US2002/0172673 are the same disclosures by Klysner et al., differing only in pagination and date of art availability.

Appellant's arguments are not persuasive for the reasons already discussed in D.

I Rejection of claims 50 and 58-65 under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Wang et al. (WO 99/67293) and in view of Rutter (US Patent 4,769,326) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant argues the same grounds as in B. Note that WO/20038 and US2002/0172673 are the same disclosures by Klysner et al., differing only in pagination and date of art availability for the reasons of record.

Appellant's arguments are not persuasive for the reasons already discussed in B.

J. Rejection of claims 8, 32-37, and 66-73 under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant argues that the rejection is improper for the reasons presented in section D.

This argument is not persuasive for the reasons already discussed in section D.

L. Rejection of claims 8, 32-37, and 66-73 under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Appellant argues that the rejection is improper for the reasons presented in section D.

This argument is not persuasive for the reasons already discussed in section D.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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/Jeffrey Stucker/
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